

Recent Advances in the Cellular and Molecular Understanding of Myelodysplastic Syndromes: Implications for New Therapeutic Approaches

Andrew M. Brunner, MD, and David P. Steensma, MD

Dr Brunner is an instructor in medicine at Harvard Medical School and an assistant in medicine at the Center for Leukemia at Massachusetts General Hospital in Boston, Massachusetts. Dr Steensma is an associate professor of medicine at Harvard Medical School and a senior physician in the Department of Medical Oncology at Dana-Farber Cancer Institute in Boston, Massachusetts.

Corresponding author:
David P. Steensma, MD, FACP
Division of Hematological Malignancies
Department of Medical Oncology
Dana-Farber Cancer Institute
450 Brookline Avenue
Boston, MA 02215
Tel: (617) 632-3712
Fax: (617) 582-7840
E-mail: David.Steensma@dfci.harvard.edu

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Abstract: It has been more than 10 years since any new disease-modifying therapies have received regulatory approval for indications related to myelodysplastic syndromes (MDS). Advances in our collective biological understanding of MDS in the last decade, however, have made it possible to hope that effective therapeutics can be designed to improve MDS-associated cytopenias and patients' quality of life, and perhaps even delay clonal progression and extend survival. Classes of MDS-associated mutations and disordered biological pathways targeted by developmental therapeutics include the following: aberrant messenger RNA splicing, neomorphic enzymes in the citric acid cycle with oncogenic activity, overactivated tyrosine and serine-threonine kinases, epigenetic and chromatin remodeling alterations, abnormal telomere dynamics, and failed protection of DNA integrity. At present, treatments for MDS are usually administered as sequential monotherapy, but there is a trend toward clinical trials of combination therapies—in which new agents are added to a DNA hypomethylating agent backbone—for both upfront treatment and the treatment of relapsed/refractory disease. Agents in clinical trials for subsets of MDS include luspatercept, antibodies targeting CD33, isocitrate dehydrogenase inhibition, deacetylase inhibitors, venetoclax, and immunotherapies designed to overcome immune-checkpoint inhibition. These biologically based therapeutics, as well as the encouraging precedent of 7 new approvals by the US Food and Drug Administration in 2017 for the treatment of acute leukemia, offer the prospect that 10 more years will not elapse before another new therapy is approved for MDS.

Introduction and Epidemiology of Myelodysplastic Syndromes

Myelodysplastic syndromes (MDS) encompass a spectrum of bone marrow malignancies characterized by cytopenias and ineffective clonal hematopoiesis, as well as a risk for evolution to acute myeloid leukemia (AML) in up to 30% of cases. It has long been recognized

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